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Trifluoromethyl ketone deriv. and phospholipase A2 inhibitor - useful in treatment of inflammatory diseases e.g. as antiinflammatory or antiallergic drug.

C97-177310

Trifluoromethyl ketone deriv. of formula $RCOCF_3$, where RCO is acyl residue of n-3 series highly unsatd. fatty acid is new.

Also claimed is the drug and/or cytoplasmic phospholipase A_2 ($cPLA_2$) inhibitor contg. trifluoromethyl ketone deriv. of formula $RCOCF_3$.

USE

The trifluoromethyl ketone deriv. is new, has phospholipase A2 inhibitory activity, and is useful as drug.

ADVANTAGE

The trifluoromethyl ketone deriv. has excellent $cPLA_2$ inhibitory activity, and is useful in treatment of inflammatory diseases e.g. as antiinflammatory or antiallergic drug.

B(10-F2, 14-C3, 14-D7A, 14-G2A) .4 B0290

PREPARATION

The trifluoromethyl ketone deriv. of formula $RCOCF_3$ can be prepd. e.g. by treatment of n-3 series highly unsatd. fatty acid with halogenating agent (e.g. oxalyl chloride) to give corresponding acid halide, followed by reaction with trifluoroacetic acid anhydride in the presence of base (e.g. pyridine) in a conventional manner (e.g. Tetrahedron Letters, 33, 1285 [1992]).

EXAMPLE

Docosahexaenic acid (164 mg) in 2 ml THF contg. half drop of DMF was reacted with 0.44 ml oxalyl chloride at room temp. for 2 hr., and the resultant acid chloride in 5 ml dichloromethane was reacted with 0.42 ml trifluoroacetic anhydride in the presence of 0.32 ml pyridine at 0°C for 1 hr. and conventionally worked up followed by chromatography over silica gel to give 56 mg (32 % yield) of docosahexaenoyltrifluoromethane ($DHA-CF_3$).

$DHA-CF_3$ and eicosapentaenoyltrifluoromethane ($EPA-CF_3$) were tested on $cPLA_2$ inhibitory activity by cell-free reaction with $cPLA_2$ in a mixt. of 1M-tris-HCl (pH 9.0), 2 % FBS-added albumin (25:12.5 µL) and 50 mM calcium chloride soln. (20 µL) at 37°C for 20 min. followed by reaction with 0.5 nmol 1-palmitoyl-2-[14C]-arachidonoyl-glycerophosphoethanolamine at 37°C for 20 min. and determination of radioactivity of free fatty acid fraction; or by cellular reaction with neutrophile (prepd. by differentiation from human myelocytic leukemia HL60 followed by cultivation in the presence of 1-[14C]-arachidonic acid) at 37°C for 5 min. in the presence of A23187 followed by determination of radioactivity of free fatty acid fraction, in comparison with arachidonoyltrifluoromethane ($AA-CF_3$) and palmitoyltrifluoromethane (PA-CF3), to give following results (Cpd., concn. (µM)/[14C]-arachidonic acid relative production (%) in: cell-free/cellular system):

None, -/100.00/100.00; $DHA-CF_3$, 1/35.2, 30/33.81; EPA-CF3, 1/28.56, 30/14.16; AA-CF3, 1/20.83, 30/21.24; and PA-CF3, 30/101.16.(PHP).

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